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Journal Pre-proof

Re: 'High prevalence of heterotopic ossification in critically ill patients with severe COVID-19' by Stoira et al

Nicolas de l'Escalopier, Laurent Mathieu, Christophe Duret, Sébastien Banzet, François Genêt, Marjorie Salga

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Re: 'High prevalence of heterotopic ossification in critically ill patients with severe COVID-19' by Stoira et al.

Nicolas de l'Escalopier^{1,2}, Laurent Mathieu^{1,3}, Christophe Duret², Sébastien Banzet^{4,5}, François Genêt^{6,7} and Marjorie Salga^{6,7}

- 1. Department of orthopedic, trauma and reconstructive surgery, Percy Military Hospital, 101 avenue Henri Barbusse, 92140 Clamart, France
- 2. CRF Les Trois Soleils, Médecine Physique et de Réadaptation, Unité de Rééducation Neurologique, Boissise-Le-Roi (77) France
- 3. Department of surgery, French Military Health Service Academy, Ecole du Val-de-Grâce, Paris, France
- 4. French Military Institute for Biomedical Research, Cell and Tissue Therapy unit, Clamart, France
- 5. Inserm UMR-MD-1197, Clamart, France
- 6. Department of Physical Medicine and Rehabilitation, CIC 1429, Raymond Poincaré Hospital, APHP, Garches, France.
- 7. END:ICAP U1179 INSERM, University of Versailles Saint Quentin en Yvelines, UFR Simone Veil-Santé, Montigny le Bretonneux, France.

^{*}Corresponding author ndelescalopier@gmail.com

Dear editor,

We would like to respond to the letter to the editor sent by Stoira et al. « High prevalence of heterotopic ossification in critically ill patients with severe COVID-19 » to give the point of view of an experienced medico-surgical team in charge of neurogenic Heterotopic Ossification (HO) case management [1].

Like Stoira et al., we have experienced a high prevalence of troublesome HO in severe COVID patients. Another rehabilitation team described HO located around the same joints after COVID [2]. Meanwhile in our service, already 3 surgeries have been performed to remove HO located around the hip. Two of them were anterior to the hip, while the third was posterior and responsible for sciatic nerve compression. Additionally, we have removed another HO of the inner elbow that was in contact with the ulnar nerve. Interestingly, development of HO in patients treated for SARS-CoV in 2003 has been reported. We believe that HO formation is likely due to the severe and prolonged inflammation experienced during intensive care, perhaps more than the virus itself [3]. Future observations of dexamethasone use to manage severe COVID patients will provide information about pathophysiological inflammatory mechanisms. HO occurs more frequently in patients who develop intensive care unit-acquired neuromuscular abnormalities, and the role of peripheral neurologic system damage has already been described for neurogenic HO [4]. Stoira et al assume that prolonged immobilization is key in HO occurrence, congruent with the observation that curare use is a risk factor for HO after severe burns [5]. Preventive physiotherapy measures have been described, including daily joint mobilization as early as possible.

They are many similarities between HO after COVID and neurogenic HO: developmental, morphological, symptoms and risks. Therefore, there is no reason not to manage COVID HO like classical neurogenic HO. The important points to consider are well defined [1]. Determining if HO is troublesome is the first step before treatment, and non-disabled patients that potentially can recover full autonomy may be more sensitive to HO sequalae. If troublesome, pain cannot be alleviated non-surgically, or signs of neural or vascular compression are present, surgery becomes necessary. Early surgery is feasible and should be performed to avoid complications. However, resection does not need to be complete as only the problematic zone of the HO mass needs to be removed. Contrast-enhanced CT with 3-dimensional reconstruction provides critical mapping of coinciding blood vessels and nerves, which is critical for determining a surgical strategy.

The report by Stoira *et al.*, establishes that HO in severe COVID patients develop more often than expected. Survivors of severe COVID that develop HO may experience complications as a result. These patients should be referred to a medico-surgical team specialized in HO for treatment, as strategies to manage HO are well established.

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- [1] Denormandie P, de l'Escalopier N, Gatin L, Grelier A, Genêt F. Resection of neurogenic heterotopic ossification (NHO) of the hip. Orthop Traumatol Surg Res 2017.
- [2] Meyer C, Haustrate M-A, Nisolle JF, Deltombe T. Heterotopic ossification in COVID-19: A series of 4 cases. Ann Phys Rehabil Med 2020.
- [3] Genêt F, Kulina I, Vaquette C, Torossian F, Millard S, Pettit AR, et al. Neurological heterotopic ossification following spinal cord injury is triggered by macrophagemediated inflammation in muscle. J Pathol 2015;236:229–40.
- [4] Debaud C, Salga M, Begot L, Holy X, Chedik M, de l'Escalopier N, et al. Peripheral denervation participates in heterotopic ossification in a spinal cord injury model. PLoS One 2017;12:e0182454.
- [5] Thefenne L, de Brier G, Leclerc T, Jourdan C, Nicolas C, Truffaut S, et al. Two new risk factors for heterotopic ossification development after severe burns. PLoS One 2017;12:e0182303.